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(54) **MEANS FOR DETECTING AND TREATING PATHOLOGIES LINKED TO FGFR3**

MITTEL ZUM NACHWEIS UND ZUR BEHANDLUNG VON KRANKHEITEN DIE IN VERBINDUNG STEHEN MIT FGFR3

MOYENS DE DETECTION ET DE TRAITEMENT DES PATHOLOGIES ASSOCIEES AU FGFR3

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(73) Proprietors:
- **Institut Curie**
  75248 Paris Cedex 05 (FR)
- **CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE (CNRS)**
  75794 Paris Cedex 16 (FR)

(72) Inventors:
- **CAPPELLEN, David**
  F-14810 Merville-Franceville (FR)
- **CHOPIN, Dominique**
  F-94000 Creteil (FR)
- **RADVANYI, François**
  F-92260 Fontenay-aux-Roses (FR)
- **RICOL, David**
  F-75013 Paris (FR)
- **THIERY, Jean-Paul**
  F-75013 Paris (FR)

(74) Representative: **Peaucelle, Chantal et al**
Cabinet Armengaud Aîné
3, Avenue Bugeaud
75116 Paris (FR)

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Description

[0001] The invention relates to means, i.e. method and drugs, for detecting and treating, respectively, pathologies linked to FGFR3 and/or to the FGFR3 pathway.

[0002] Fibroblast growth factor receptor 3 (FGFR3) belongs to a family of structurally related tyrosine kinase receptors (FGFRs 1-4) encoded by four different genes. These receptors are glycoproteins composed of two to three extracellular immunoglobulin (Ig)-like domains, a transmembrane domain and a split tyrosine-kinase domain. Alternative mRNA splicing results in many different receptors variants. Isoforms FGFR3-IIIb and FGFR3-IIIc result from a mutually exclusive splicing event in which the second half of the juxtamembrane Ig-like domain is encoded either by the 151 nucleotides long exon 8 (IIIb variant) or the 145 nucleotides long exon 9 (IIIc variant).

[0003] Specific point mutations in the *FGFR3* gene which affect different domains of the protein are associated with autosomal dominant human skeletal disorders such as hypochondroplasia, achondroplasia, severe achondroplasia with developmental delay and acanthosis nigricans and thanatophoric dysplasia. Several reports have demonstrated that these mutations lead to constitutive activation of the receptor. Taking into account this result, together with the skeletal overgrowth observed in mice homozygous for null alleles of *Fgfr3*, FGFR3 appears as a negative regulator of bone growth.

[0004] In contrast with this inhibitory role, an oncogenic role has been proposed for *FGFR3* in multiple myeloma (MM) development. In this malignant proliferation of plasma cells, a t(4;14)(p16.3;q32.3) chromosomal translocation with breakpoints located 50 to 100 Kb centromeric to *FGFR3* is present in 20-25% of the cases and is associated with overexpression of FGFR3.

[0005] In very rare cases (2 out of 12 MM cell lines and 1 out of 85 primary MM tumours), activating mutations of *FGFR3* previously identified in human skeletal disorders have been found, but always accompanied by the t(4;14)(p16.3; q32.3) translocation.

[0006] By investigating various cancers, the inventors have surprisingly found a role for FGFR3 in cancers originating from epithelial tissues, carcinomas.

[0007] The involvement of FGFR3 in such solid tumour development is linked to a constitutional activation : it may be activated by an autocrinal loop (ligand self-production) and/or by activating mutations in *FGFR3.* Surprisingly, such mutations are found in primary tumours and are somatic mutations (genomic DNA mutations).

[0008] So far, the only FGFR3 isoform which has been identified in epithelium is the FGFR3-IIIb isoform.

[0009] The invention thus relates to a method and kits for detecting carcinomas.

[0010] According to another aspect, the invention also relates to the manufacture of drugs capable of treating carcinomas.

[0011] According to still another aspect, it relates to transgenic animals enabling the efficiency of such drugs to be tested.

[0012] The method of the invention for detecting carcinomas in a biological sample comprises identifying FGFR3 mutations.

[0013] Standard methods can apply for such an identification such as immunohistochemistry, or detection of the corresponding RNA, DNA, and encoded protein contained in said sample, particularly after extraction thereof. A common way for such a detection comprises amplifying by PCR, RT-PCR or RT-PCR SSCP (single strand conformation polymorphism) with *FGFR3* specific primers and revealing the amplification products according to the usual methods. A corresponding embodiment is exemplified in the examples given hereinafter. Another common way comprises the use of antibodies and the detection of the antigen-antibody reaction with appropriate labelling.

[0014] The activating function of a mutation can be determined by observation of activating signals such as receptor phosphorylation, cell proliferation (e.g. thymidine incorporation) or indirect effects such as calcium influx, phosphorylation of target sequences.

[0015] More particularly, said identification comprises screening for single nucleotide mutation(s) in the genomic DNA and/or its products, i.e. RNA, protein, the term "product" also encompassing cDNA.

[0016] Particularly, said method comprises screening for mutations creating cysteine residues in the extracellular or transmembrane domains of the receptor.

[0017] Alternatively, or in combination with the foregoing embodiment, it comprises screening for mutations resulting in at least one amino-acid substitution in the kinase domain of the receptor.

[0018] It particularly comprises screening of activating mutation(s) of FGFR3, notably such as above-described.

[0019] More particularly, the method of the invention comprises screening for mutation(s) in exon 7, encoding the junction between immunoglobulin-like domains II and III of FGFR3, in exon 10, encoding the transmembrane domain, in exon 15, encoding the tyrosine kinase domain I, and/or in the exon encoding the C-terminal part.

[0020] Advantageously, the method of the invention comprises screening for missense mutations such as implicated in thanatophoric dysplasia, NSC, achondroplasia, saddan, or hypochondroplasia.

[0021] Such FGFR3 mutations notably comprise R248C, S249C, G372C, S373C, Y375C, K652E, K652M, J809G, J809C, J809R, J809L, P250R, G377C, G382R, A393E, N542K (codons are numbered according to FGFR3-IIIb cDNA open reading frame).

[0022] The following FGFR3 mutations will be particularly identified : R248C, S249C, G372C, K652E and Y375C.

[0023] Said biological sample used in the method of the invention will advantageously comprise a tissue, bone marrow, or a fluid such as blood, urine, deriving from a warm-blooded animal, and more especially from a human.

[0024] Said method is particularly useful for detecting carcinomas, such as human bladder and cervix carcinomas. A major issue in superficial bladder cancer is to distinguish tumours which will progress from those which will not. Insights into the genetic and epigenetic alterations involved in bladder cancer is expected to provide useful information to facilitate this distinction. In that respect, the invention provides means to resolve the dilemma between a bladder-sparing strategy versus cystectomy and will contribute to a more individualised intravesical instillation and endoscopic monitoring policy.

[0025] Indeed, as shown by the results given in the examples, *FGFR3* appears to be a major oncongene in Ta, T 1 bladder carcinomas. The *FGFR3* mutations appear to be frequently associated with tumours that do not progress. Multivariate analysis showed that *FGFR3* mutation status remained a statistically significant predictor of good outcome. *FGFR3* mutations thus provide clear-cut information, which may complement stage and grade. The use of these mutations alone and/or in combination with other predictors of tumour aggressiveness will then provide relevant prognostic information.

[0026] Said method, will also be used for detecting for example lung, breast, colon, skin cancers.

[0027] The method of detection according to the invention applies to the diagnostic of carcinomas, as well to the prognosis, or the follow-up of the efficiency of a therapy.

[0028] Said method will advantageously be performed by using kits comprising the appropriate reagents and a notice of use.

[0029] According to another aspect, the invention relates to the manufacture of drugs having an anti-proliferative effect on carcinoma cells. Such drugs comprise, as active principle(s) agent(s) which act by inhibition of FGFR3 DNA synthesis or by inhibition of its expression products (RNA, proteins). Particularly, such drugs contain tyrosine kinase inhibitors specific for FGFR3.

[0030] Other appropriate inhibitors comprise antibodies directed against FGFR3, and particularly against at least one extracellular Ig-like domain thereof. Advantageously said antibodies are specific for FGFR3-IIIb. Preferred antibodies are monoclonal ones, and particularly antibodies modified so that they do not induce immunogenic reactions in a human body (e.g. humanized antibodies).

[0031] Other appropriate inhibitors comprise antisens oligonucleotides directed against a wild or mutated *FGFR3* isoform.

[0032] The administration and the posology of said inhibitors will be determined by the one skilled in the art depending on the carcinoma to be treated, the weight and age of the patient. For example, antibodies will be administered by the injectable route.

[0033] The invention thus gives means of great interest for detecting and treating carcinomas, taking into account the fact that cancers originating from epithelial tissues (carcinomas) represent approximately 90 % of malignant neoplasms.

[0034] Disclosed are cell lines capable of expressing FGFR3 mutated forms. Particularly, disclosed are FGFR3 S249C mutated forms. T24 cell lines constitutively expressing FGFR3 S249C mutated forms and HeLa cell lines expressing FGFR3 S249C mutated forms in an inducible manner have thus been obtained (for example see ref.(6)).

[0035] By injecting such cell lines to nude mice, an increased tumorigenicity was observed.

[0036] Such cell lines are useful *in vitro* (follow up of the receptor phosphorylation) or *in vivo* (examination of the tumorigenicity of nude mice) to study the inhibitor effect against FGFR3.

[0037] Cell lines transfected with FGFR2, FGFR1 or FGFR4 are particularly useful for studying the specificity of inhibitors to be tested.

[0038] According to still another object, the invention relates to constructions capable of expressing by transgenesis a FGFR3 mutated form in epitheliums and the transgenic animals thus obtained which are characterized by the fact that they comprise such constructions.

[0039] Examples of constructions intended for injection in animal germinal cells comprise a keratin promoter, particularly keratin 14 promoter and cDNA of mutated FGFR3.

[0040] Other advantages and characteristics of the invention will be given in the following examples wherein it will be referred to

- figures 1A - 1B which give FGFR3-IIIb gene activating mutations in primary tumours,
- figures 2A - 2E which refer to FGFR3-IIIb wild (2A) and mutated pro-oncogenic (2B-2T) sequences. It will be noted that the sequences of figures 2B to 2T, as such, enter into the scope of the invention. There may be silent polymorphisms all along the sequence, so there may be in fact several possible sequences for each mutant, and
- figures 3a and 3b which respectively represent a) Kaplan-Meier progression-free survival curves according to *FGFR3* mutations (dotted line: mutated *FGFR3,* solid line: non-mutated *FGFR3;* log rank test p=0.014) ; b) Kaplan-Meier disease-specific survival curves according to *FGFR3* mutations (dotted line: mutated *FGFR3,* solid line: non-mutated *FGFR3;* log rank test p=0.007)

Example 1 *: FGFR3* gene mutations in bladder and cervix carcinomas

[0041] *FGFR3-IIIb* and *FGFR3-IIIc* transcript levels were examined by reverse transcription-polymerase chain reaction (RT-PCR) in 76 primary bladder carcinomas and 29 primary invasive cervical carcinomas.

[0042] *FGFR3-IIIb,* the sole isoform to be significantly expressed, was detected in 72 out of 76 (94%) bladder carcinomas and 27 out of 29 (93%) cervical carcinomas.

[0043] A PCR-SSCP analysis was then conducted on both reverse transcribed RNA and genomic DNA to screen for *FGFR3* coding sequence variants in 26 bladder and 12 cervix cancers expressing the gene. The results are illustrated in figures 1a and 1b which gives the identification of *FGFR3* gene mutations in human carcinomas :

- a: gives the identification of somatic mutations by direct sequencing of PCR products. Normal constitutional DNA; Tumour, tumour DNA.
- b: gives FGFR3 mutations associated with squeletal disorders and cancers.

[0044] The schematic structure of FGFR3 is depicted (Ig I-III, immunoglobulin like domains ; TM, transmembrane domain ; TK-1 and -2, tyrosine kinase domains) and the locations of the known human missense mutations associated with thanatophoric dysplasia (TD) and severe achondroplasia (SADDAN), bladder and cervix carcinomas (carc.) and multiple myeloma (MM) are indicated. Usual amino acid abbreviations are used to point out the mutation found in each pathological situation. The mutations at codon 807 incriminated in TD replaces a Stop codon (J) by an amino acid (G, C, R or L) and the mRNA thus continues to be translated until another in-frame Stop codon is reached 423 nucleotides downstream thus leading to a 141 amino acid longer protein.

[0045] Abnormally migrating bands were observed for certain samples (Fig. la) and direct sequencing of PCR products revealed single nucleotide substitutions in 9 out 26 bladder carcinomas (35 %) and 3 out of 12 (25 %) cervix carcinomas (Fig. 1b and table 1).

Table 1

Summary of FGFR3 gene mutations in primary bladder and cervix cancers

Sample	Histopathol.	Codon	Nt Position	Mutation	Predicted effect
1447, bladder	carc., Ta G2	249	746	TCC to TGC	Ser to Cys
342, bladder	carc., Tla G1	249	746	TCC to TGC	Ser to Cys
813, bladder	carc., Tla G1	372	1114	GGC to TGC	Gly to Cys
1393.1, bladder	carc., Tla G3	249	746	TCC to TGC	Ser to Cys
506, bladder	carc., Tlb G2	372	1114	GGC to TGC	Gly to Cys
1084, bladder	carc., Tlb G3	652	1954	AAG to GAG	Lys to Glu
745.1, bladder	carc., T2 G3	248	742	CGC to TGC	Arg to Cys
1077, bladder	carc., T3 G2	249	746	TCC to TGC	Ser to Cys
1210, bladder	carc., T3 G2	249	746	TCC to TGC	Ser to Cys
4.13, cervix	carc., stage II	249	746	TCC to TGC	Ser to Cys
4.139, cervix	carc., stage II	249	746	TCC to TGC	Ser to Cys
6.96.1, cervix	carc., stage II	249	746	TCC to TGC	Ser to Cys

Histopathol., histopathological classification of the tumours (carc., carcinoma: TNM and HUGO classifications are used respectively for bladder and cervix cancers) ; codon and mutated nucleotide (Nt position) are numbered according to FGFR3-IIIb cDNA open reading frame.

[0046] Mutations were found in the following exons

- exon 7, encoding the junction between immunoglobulin-like domains II and III of FGFR3 (one C-to-T transition at codon 248 in patient 745.1 and a C-to-G substitution at codon 249 in patient 1447) ;
- exon 10, encoding the transmembrane domain (a G-to-T-transversion at codon 372 in patient 813)
- exon 15, encoding the tyrosine kinase domain II (a A-to-G transition at codon 652 in patient 1084).

[0047] Analysis of matched constitutional DNA from the patients for which such material was available (n=8) demonstrated the somatic nature of these *FGFR3* mutations (Figure 1).

[0048] Strikingly, each of the FGFR3 missense mutations identified herein, i.e. R248C. S249C. G372C and K652E.

are implicated in thanatophoric dysplasia (TD). Given the presence of two additional amino-acids in the IIIb isoform expressed in epithelial cancers as compared to the IIIc isoform expressed in bone, the G372C and K652E mutations are indeed equivalent to the G370C and K650E mutations responsible for TD.

[0049] The S249C mutation was the most commonly observed, affecting 5 out of 9 (55 %) bladder cancers and all of the cervical cancers (3 out of 3, 100 %) in which *FGFR3* gene alterations have been identified so far.

[0050] The R248C, S249C and G372/370C mutations create cysteine residues in the extracellular or transmembrane domains of the receptor and the K652/650E mutations results in amino-acid substitution in the kinase domain of the receptor.

Example 2 : Inhibitors

[0051] A way to test the different FGFR3 inhibitors comprises transfecting cell lines so that they express the mutated forms of FGFR3, or wild type FGFR3 or just the neomycin or hygromycin resistant gene under the control of a strong promoter, such as CMV, RSV, SV40 promoters. The tumorigenic properties of these cell lines can then be compared *in vitro* or *in vivo* in nude mice. The different inhibitors will be tested *in vitro* or *in vivo* using these different cell lines. Phosphorylation, proliferation or indirect effects of FGFR3 such as calcium influx will be measured. Transgenic mice expressing in various epithelia the mutated FGFR3 can thus be derived thereof. Those mice developping tumours are useful tools for testing the efficiency of candidate inhibiting drugs. Such transgenic animals fall also into the scope of the present invention.

Example 3 : FGFR3 mutations in Ta, T1 tumours in bladder cancer.

[0052] Bladder cancer is a disease with a spectrum of forms and is highly unpredictable. At the time of initial diagnosis, approximately 80% of patients present with a superficial tumour. Superficial bladder cancers include carcinoma *in situ* (Tis), Ta and T1 lesions (TNM classification). Ta/T1 lesions are mostly papillary urothelial carcinomas: Ta lesions do not invade the basement membrane, whereas T1 lesions invade the lamina propria, but do not invade the detrusor muscle of the bladder wall. Carcinoma *in situ* are flat, cytologically high-grade carcinomas, confined to the urothelium. Primary isolated carcinoma *in situ* is a very rare entity and is more commonly associated with Ta/T1 lesions. Despite transurethral resection alone or combined with adjuvant intravesical therapies, more than one half of patients with Ta/T1 tumours suffer recurrences. In most cases, recurrences are also superficial, but about 5% of Ta and 30-50% of T1 tumours progress in an unpredictable manner to muscle invasion with a high risk of development of metastases and death from bladder cancer.

[0053] The management of superficial bladder cancer is based on clinicopathological parameters. Three groups of tumours can be defined. of low, intermediate and high risk, according to their potential for recurrence and progression. This classification is used to recommend adjuvant intravesical therapies and bladder monitoring, but it is not a sufficiently sensitive discriminant for use in determining the appropriate treatment and mode of surveillance for a given patient. Although Bacille Calmette-Guérin (BCG) therapy appeared to be the most effective regimen for the high-risk group, long-term results indicate that progression occurs in 40% by 10 years and in more than 50% by 15 years. For some researchers, these findings justified the use of up-front radical cystectomy in high-risk superficial urothelial carcinomas, despite the risk of overtreating a significant number of patients. Follow-up of Ta and T1 superficial bladder cancers constitutes most of the workload of urologists involved in the management of bladder cancer. The current strategy is based on frequent cystoscopic evaluations using a schedule that is largely empirical, without considering the individual characteristics of the tumour.

[0054] The limitations of the current management of bladder cancer demonstrate the need for prognostic markers, making possible the use of selective aggressive treatments for patients at high risk of progression while sparing low-risk patients from unnecessary procedures. A number of chromosomal loci and specific genes have been implicated in bladder tumorigenesis. Losses of all or part of chromosome 9 in many TaG1 tumours suggests that the inactivation of a gene or genes on chromosome 9 may be an early event in urothelial transformation. The prognostic significance of losses on chromosome 9 is unclear. Alterations of the *P53* and *RB* genes controlling the G1 cell cycle checkpoint have been clearly delineated and are associated with the aggressiveness of superficial and invasive bladder cancers. Despite these recent insights into the molecular mechanisms of bladder carcinoma progression, these markers have not yet had any impact on clinical practice.

[0055] The following assays have been performed to assess the reliability, as markers, of the FGFR3 mutations.

Material and method

Patients and tissue samples

[0056] Seventy four specimens of superficial Ta, T1 bladder carcinomas were obtained from 74 patients by transurethral resection performed at the Henri Mondor hospital, Créteil, France, from January 1988 to December 1998. Tumours were staged according to the TNM classification (1) and graded according to criteria recommended by the World Health Organisation (2). This series consisted of 25 pTa and 49 pT1 tumours, with 28 grade G1, 33 grade G2 and 13 grade G3 tumours. The 64 men and 10 women had a mean age of 64 years (range: 29 to 94 years). None of the patients had any detectable distant metastases at the time of transurethral resection. Patients were treated by transurethral resection (TUR) alone (n=25), TUR followed by mitomycin C instillation (n=10) or TUR and BCG (n=39) according to the French Committee for Urologic Oncology (CCAFU) recommendations. There was no change in the policy for treating superficial bladder cancer during the study period. Progression was defined as the occurrence of a pT2 or higher stage or appearance of lymph node invasion or metastasis or death from cancer. Disease-specific survival curves were plotted using death from urothelial cancer as the endpoint. Follow-up was based on systematic cystoscopy and cytology, and imaging studies only when indicated. All outpatient visits and hospital admissions were recorded in a database from which the study data were calculated.

[0057] Tumour DNA was extracted from formalin-fixed and paraffin-embedded tissue or samples freshly frozen in liquid nitrogen (4). Normal DNA samples from peripheral blood were available for 27 patients.

FGFR3 mutation analysis

[0058] Mutations in the *FGFR3* gene were detected by SSCP analysis. Exons 7, 10, 15 and 20 of the *FGFR3* gene were analysed because these exons harbour all the mutations previously identified in bladder carcinomas and thanatophoric dysplasia. All mutations detected by SSCP analysis were confirmed by direct bidirectional sequencing of tumour genomic DNA. Matched normal DNA, if available, was sequenced on both strands to demonstrate the somatic nature of these mutations.

Statistical methods

[0059] Associations between *FGFR3* mutation status and other data (sex, age, stage and grade) were tested using χ^2 and Student's t tests. Progression-free and disease-specific survival curves were plotted using Kaplan-Meier estimates. Survival distributions were compared using the log-rank test. Cox's proportional hazards regression model was used to test the effect of mutations, while simultaneously accounting for baseline patient and tumour characteristics. The influence of the covariates on the *FGFR3* mutation effect was assessed in multivariate analysis involving a forward stepwise procedure and a backward stepwise procedure, using the MPRL (maximum partial likelihood ratio) method. The limit to enter a term was 0.15 and the limit to remove a term was 0.10. Statistical analyses were performed using BMDP® and S-Plus® software.

Results

[0060] *FGFR3* missense mutations were observed in 41 of the 74 (55%) Ta, T1 bladder tumours. The *FGFR3* mutations found are described in Table 2 below :

Table 2

Number of tumours (%)	Codon*	nt position*	Mutation	Predicted effect
5(12%)	248	742	CGC -> TGC	Arg -> Cys
28(68.5%)	249	746	TCC -> TGC	Ser -> Cys
5(12%)	372	1,114	GGC -> TGC	Gly -> Cys
2(5%)	375	1,124	TAT -> TGT	Tyr -> Cys
1 (2.5%)	652	1,954	AAG -> GAG	Lys -> Glu
* codon and mutated nucleotide (nt position) are numbered according to FGFR3-IIIb cDNA open reading frame. FGFR3-IIIb is the isoform expressed in epithelial cells.				

[0061] S249C was the commonest mutation and was found in 16 of the 21 (76%) mutated Ta tumours and 12 of the 20 (60%) mutated T1 tumours. Matched constitutional DNA, available in 15 of the cases of tumour with mutations, contained wild-type sequences, demonstrating the somatic nature of these mutations.

[0062] The correlation between sex, age, stage, grade and *FGFR3* mutation status is given Table 3 :

Table 3

	FGFR3 wild type	*FGFR3* mutant	p value (χ^2 or Student's t test)
Sex			
Male	29	35	
Female	4	6	0.9779
Age (years)			
mean	64.30	63.22	
range	[29.15-86.10]	[34.3-94.4]	0.7393
Stage			
Ta	4	21	
T1	29	20	0.001
Grade			
G1	7	21	
G2	14	19	
G3	12	1	0.0003

[0063] Statistically significant correlations were observed between *FGFR3* mutations and low stage (p=0.001) and low grade (p=0.0003), but not between these mutations and age or sex (Table 2).

[0064] With a median follow-up of 4.3 years (range: 6 months to 11 years), 3 patients progressed and one died in the mutated tumour group (n=41 patients) whereas ten patients progressed and eight died in the non-mutated tumour group (n=33 patients). The median follow-up was 5.6 years (range: 7 months to 11 years) in the non-mutated group and 4.1 years (range: 6 months to 9 years) in the mutated group.

[0065] To examine *FGFR3* mutations as a marker of patient outcome, we calculated Kaplan-Meier progression-free survival and disease-specific survival probability curves for the two groups of patients and examined the differences using the log rank test. Progression-free and disease-specific survival indicated that *FGFR3* mutations were associated with a lower risk of progression (p=0.014) and longer survival (p=0.007) (Figure 3). We tested several variables (age, sex, stage, grade) but only stage was significantly associated with progression and survival in univariate analysis. If only T1 patients were analysed, the correlation was still significant for disease-specific survival (p=0.03) and close to significance for progression-free survival (p=0.052).

[0066] Multivariate analysis was used to determine whether the correlation between *FGFR3* mutation status and progression-free survival or disease-specific survival was independent of other outcome predictors. For progression-free survival, the following covariates were introduced into the Cox model: mutation, stage, grade and sex. For disease-specific survival, mutation and grade were the only covariates introduced into the model, as no disease-related deaths were observed among female or Ta patients. If *FGFR3* status was entered into the model, neither stage nor grade provided any additional prognostic value for tumour progression. In the analysis of disease-specific survival, *FGFR3* mutation was also the only covariate to be entered into the model, as grade did not provide any additional prognostic information. Relative risks and their 95% confidence intervals (CI) are shown in Table 4.

Table 4

	Progression		Disease-specific Survival	
	Relative Risk	95% CI	Relative Risk	95% CI
FGFR3				
Wild-type	1		1	
Mutant	0.23	(0.06; 0.83)	0.10	(0.01; 0.80)

(continued)

	Progression		Disease-specific Survival	
	Relative Risk	95% CI	Relative Risk	95% CI
Other variables do not significantly contribute to the model				
Forward and backward procedures both yielded the same model. As shown by the above results, the FGFR3 activating mutations were frequent in bladder carcinomas.				

[0067] All the carcinomas having a mutated receptor expressed said receptor at levels similar or above those observed with normal tissues. Immunohistochemical methods will then advantageously be used for revealing the receptor.

[0068] FGFR3 mutation detection in bladder carcinomas appears to be a good pronostic, giving then to the clinicians valuable means for treating and observing carcinomas, which represent a medical problem due to the high frequency of recurrences.

[0069] By using SSCP or PCR coupled to an enzymatic restriction S249C mutation specific (which represent 75% of the mutations) on patients having bladder carcinomas with S249C mutation, the mutation could be detected in urine in 60% of the cases.

Example 4: Detection of FGFR3 mutations in patients' urines

[0070] Genomic DNA is extracted from patients' urines and amplified by PCR, in the presence of ^{32}P- labelled dCTP, using standard methods. The following primers were used for detecting S249C mutation :
5'-CAG CAC CGC CGT CTG GTT GG-3' and 5'-AGT GGC GGT GGT GGT GAG GGA G-3'.
30 cycles of PCR are performed.
The amplification products are digested by *Cac8I.* An additional site is created by *FGFR3* mutation and a corresponding band is observed on an electrophoretic gel.

[0071] Similarly the following primers and enzymes can be used to detect:

R248C mutation:
Primers : 5'-TGT GCG TCA CTG TAC ACC TTG CAG-3' and 5'-AGT GGC GGT GGT GGT GAG GGA G-3'
Enzyme : *Bsi* HKA I

K652E mutation :
Primers : 5'-TGG TGA CCG AGG ACA ACG TGA TG-3' and 5'-AGG GTG TGG GAA GGC GGT GTT G-3'
Enzyme : *Bsm* A I

G372C mutation:
Primers : 5'-CCT CAA CGC CCA TGT CTT TTC AGC-3' and 5'-CTT GAG CGG GAA GCG GGA GAT CTT G-3'
Enzyme: *Pst* I

Y375C mutation:
Primers : 5'-CCT CAA CGC CCA TGT CTT TTC AGC-3' and 5'-CTT GAG CGG GAA GCG GGA GAT CTT G-3'
Enzyme: *Bsg* I

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[0072]

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5. Cappellen D, De Oliveira C, Ricol D, Gil Diez de Medina S, Bourdin J, Sastre-Garau X, Chopin D, Thiery JP, Radvanyi F. Frequent activating mutations of FGFR3 in human bladder and cervix carcinomas. *Nature Genetics*, vol 23, sept. 1999.

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LISTE DE SEQUENCES

[0073]

<110> INSTITUT CURIE
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<120> DETECTION AND TREATMENT OF PATHOLOGIES LINKED TO FGFR3.

<130> 59743-1143

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<141> 2000-05-04

<150> US 60/132,705
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agctccagct cctcagggga cgactccgtg tttgcccacg acctgctgcc cccggcccca 2400
cccagcagtg ggggctcgcg gacgtga 2427

<210> 6
<211> 2427

<212> ADN
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Mutant S373C FGFR3-IIIb:

<400> 6

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ccagagcccg gccagcagga gcagttggtc ttcggcagcg gggatgctgt ggagctgagc 180
tgtcccccgc ccgggggtgg tcccatgggg cccactgtct gggtcaagga tggcacaggg 240
ctggtgccct cggagcgtgt cctggtgggg ccccagcggc tgcaggtgct gaatgcctcc 300
cacgaggact ccggggccta cagctgccgg cagcggctca cgcagcgcgt actgtgccac 360
ttcagtgtgc gggtgacaga cgctccatcc tcgggagatg acgaagacgg ggaggacgag 420
gctgaggaca caggtgtgga cacagggccc ccttactgga cacggcccga gcggatggac 480
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<210> 7
<211> 2427
<212> ADN
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Mutant Y375C FGFR3-IIIb:

<400> 7

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ccagagcccg gccagcagga gcagttggtc ttcggcagcg gggatgctgt ggagctgagc 180
tgtccccccgc ccgggggtgg tcccatgggg cccactgtct gggtcaagga tggcacaggg 240
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gctgaggaca caggtgtgga cacaggggcc ccttactgga cacggcccga gcggatggac 480
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cccagcagtg ggggctcgcg gacgtga 2427

<210> 8
<211> 2427
<212> ADN
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Mutant K652M FGFR3-IIIb:

<400> 8

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ccagagcccg gccagcagga gcagttggtc ttcggcagcg gggatgctgt ggagctgagc 180
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ctggtgccct cggagcgtgt cctggtgggg ccccagcggc tgcaggtgct gaatgcctcc 300
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ttcagtgtgc gggtgacaga cgctccatcc tcgggagatg acgaagacgg ggaggacgag 420
gctgaggaca caggtgtgga cacaggggcc ccttactgga cacggcccga gcggatggac 480
aagaagctgc tggccgtgcc ggccgccaac accgtccgct tccgctgccc agccgctggc 540
aaccccactc cctccatctc ctggctgaag aacggcaggg agttccgcgg cgagcaccgc 600
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cccagcagtg ggggctcgcg gacgtga 2427

<210> 9
<211> 2427
<212> ADN
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Mutant X809C FGFR3-IIIb:

<400> 9

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cccagcagtg ggggctcgcg gacgtgc 2427

<210> 10
<211> 2427
<212> ADN
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Mutant X809G FGFR3-IIIb:
(Mutant 1)

<400> 10

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ccagagcccg gccagcagga gcagttggtc ttcggcagcg gggatgctgt ggagctgagc 180
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cccagcagtg ggggctcgcg gacggga                                      2427
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<210> 11
<211> 2427
<212> ADN
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Mutant X809G FGFR3-IIIb:
(Mutant 2)

<400> 11

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ccagagcccg gccagcagga gcagttggtc ttcggcagcg gggatgctgt ggagctgagc 180
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ctggtgccct cggagcgtgt cctggtgggg ccccagcggc tgcaggtgct gaatgcctcc 300
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ttcagtgtgc gggtgacaga cgctccatcc tcgggagatg acgaagacgg ggaggacgag 420
gctgaggaca caggtgtgga cacaggggcc ccttactgga cacggcccga gcggatggac 480
aagaagctgc tggccgtgcc ggccgccaac accgtccgct tccgctgccc agccgctggc 540
aaccccactc cctccatctc ctggctgaag aacggcaggg agttccgcgg cgagcaccgc 600
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tcggaccgcg gcaactacac ctgcgtcgtg gagaacaagt ttggcagcat ccggcagacg 720
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ctgtcggacc tggtgtctga gatggagatg atgaagatga tcgggaaaca caaaaacatc 1620
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gctgcccgca atgtgctggt gaccgaggac aacgtgatga agatcgcaga cttcgggctg 1920
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cctgtggagg agctcttcaa gctgctgaag gagggccacc gcatggacaa gcccgccaac 2160
tgcacacacg acctgtacat gatcatgcgg gagtgctggc atgccgcgcc ctcccagagg 2220
cccaccttca agcagctggt ggaggacctg gaccgtgtcc ttaccgtgac gtccaccgac 2280
gagtacctgg acctgtcggc gcctttcgag cagtactccc cgggtggcca ggacacccca 2340
agctccagct cctcagggga cgactccgtg tttgcccacg acctgctgcc cccggcccca 2400
cccagcagtg ggggctcgcg gacgaga                                     2427
```

<210> 12
<211> 2427
<212> ADN
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Mutant X809G FGFR3-IIIb:
(Mutant 3)

<400> 12

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tcctcggagt ccttggggac ggagcagcgc gtcgtggggc gagcggcaga agtcccgggc 120
ccagagcccg gccagcagga gcagttggtc ttcggcagcg gggatgctgt ggagctgagc 180
tgtccccccgc ccggggggtgg tcccatgggg cccactgtct gggtcaagga tggcacaggg 240
ctggtgccct cggagcgtgt cctggtgggg ccccagcggc tgcaggtgct gaatgcctcc 300
cacgaggact ccgggggcta cagctgccgg cagcggctca cgcagcgcgt actgtgccac 360

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gctgaggaca caggtgtgga cacaggggcc ccttactgga cacggcccga gcggatggac 480
aagaagctgc tggccgtgcc ggccgccaac accgtccgct tccgctgccc agccgctggc 540
aaccccactc cctccatctc ctggctgaag aacggcaggg agttccgcgg cgagcaccgc 600
attggaggca tcaagctgcg gcatcagcag tggagcctgg tcatggaaag cgtggtgccc 660
tcggaccgcg gcaactacac ctgcgtcgtg gagaacaagt ttggcagcat ccggcagacg 720
tacacgctgg acgtgctgga gcgctccccg caccggccca tcctgcaggc ggggctgccg 780
gccaaccaga cggcggtgct gggcagcgac gtggagttcc actgcaaggt gtacagtgac 840
gcacagcccc acatccagtg gctcaagcac gtggaggtga acggcagcaa ggtgggcccg 900
gacggcacac cctacgttac cgtgctcaag tcctggatca gtgagagtgt ggaggccgac 960
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gccgaggagg agctggtgga ggctgacgag gcgggcagtg tgtatgcagg catcctcagc 1140
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ctgtcggacc tggtgtctga gatggagatg atgaagatga tcgggaaaca caaaaacatc 1620
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gccaagggta acctgcggga gtttctgcgg gcgcggcggc ccccgggcct ggactactcc 1740
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aagtggatgg cgcctgaggc cttgtttgac cgagtctaca ctcaccagag tgacgtctgg 2040
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cctgtggagg agctcttcaa gctgctgaag gagggccacc gcatggacaa gcccgccaac 2160
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cccaccttca agcagctggt ggaggacctg gaccgtgtcc ttaccgtgac gtccaccgac 2280
gagtacctgg acctgtcggc gcctttcgag cagtactccc cgggtggcca ggacacccca 2340
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cccagcagtg ggggctcgcg gacgcga                                     2427
```

<210> 13
<211> 2427
<212> ADN
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Mutant X809L FGFR3-IIIb:

<400> 13

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tcctcggagt ccttggggac ggagcagcgc gtcgtggggc gagcggcaga agtcccgggc 120
ccagagcccg gccagcagga gcagttggtc ttcggcagcg gggatgctgt ggagctgagc 180
tgtcccccgc ccgggggtgg tcccatgggg cccactgtct gggtcaagga tggcacaggg 240
ctggtgccct cggagcgtgt cctggtgggg ccccagcggc tgcaggtgct gaatgcctcc 300
cacgaggact ccggggccta cagctgccgg cagcggctca cgcagcgcgt actgtgccac 360
ttcagtgtgc gggtgacaga cgctccatcc tcgggagatg acgaagacgg ggaggacgag 420
gctgaggaca caggtgtgga cacaggggcc ccttactgga cacggcccga gcggatggac 480
aagaagctgc tggccgtgcc ggccgccaac accgtccgct tccgctgccc agccgctggc 540
aaccccactc cctccatctc ctggctgaag aacggcaggg agttccgcgg cgagcaccgc 600
attggaggca tcaagctgcg gcatcagcag tggagcctgg tcatggaaag cgtggtgccc 660
tcggaccgcg gcaactacac ctgcgtcgtg gagaacaagt ttggcagcat ccggcagacg 720
tacacgctgg acgtgctgga gcgctccccg caccggccca tcctgcaggc ggggctgccg 780
gccaaccaga cggcggtgct gggcagcgac gtggagttcc actgcaaggt gtacagtgac 840
gcacagcccc acatccagtg gctcaagcac gtggaggtga acggcagcaa ggtgggcccg 900
gacggcacac cctacgttac cgtgctcaag tcctggatca gtgagagtgt ggaggccgac 960
gtgcgcctcc gcctggccaa tgtgtcggag cgggacgggg gcgagtacct ctgtcgagcc 1020
accaatttca taggcgtggc cgagaaggcc ttttggctga gcgttcacgg gccccgagca 1080
gccgaggagg agctggtgga ggctgacgag gcgggcagtg tgtatgcagg catcctcagc 1140
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ctgtcggacc tggtgtctga gatggagatg atgaagatga tcgggaaaca caaaaacatc 1620
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taccaggtgg cccggggcat ggagtacttg gcctcccaga agtgcatcca cagggacctg 1860
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cctgtggagg agctcttcaa gctgctgaag gagggccacc gcatggacaa gcccgccaac 2160
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gagtacctgg acctgtcggc gcctttcgag cagtactccc cgggtggcca ggacaccccc 2340
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cccagcagtg ggggctcgcg gacgtta 2427

<210> 14
<211> 2427
<212> ADN
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Mutant N542K FGFR3-IIIb:
(Mutant 1)

<400> 14

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tcctcggagt ccttggggac ggagcagcgc gtcgtggggc gagcggcaga agtcccgggc 120
ccagagcccg gccagcagga gcagttggtc ttcggcagcg gggatgctgt ggagctgagc 180
tgtcccccgc ccgggggtgg tcccatgggg cccactgtct gggtcaagga tggcacaggg 240
ctggtgccct cggagcgtgt cctggtgggg ccccagcggc tgcaggtgct gaatgcctcc 300
cacgaggact ccggggccta cagctgccgg cagcggctca cgcagcgcgt actgtgccac 360
ttcagtgtgc gggtgacaga cgctccatcc tcgggagatg acgaagacgg ggaggacgag 420
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aagaagctgc tggccgtgcc ggccgccaac accgtccgct tccgctgccc agccgctggc 540
aaccccactc cctccatctc ctggctgaag aacggcaggg agttccgcgg cgagcaccgc 600
attggaggca tcaagctgcg gcatcagcag tggagcctgg tcatggaaag cgtggtgccc 660
tcggaccgcg gcaactacac ctgcgtcgtg gagaacaagt ttggcagcat ccggcagacg 720
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gccaaccaga cggcggtgct gggcagcgac gtggagttcc actgcaaggt gtacagtgac 840
gcacagcccc acatccagtg gctcaagcac gtggaggtga acggcagcaa ggtgggcccg 900
gacggcacac cctacgttac cgtgctcaag tcctggatca gtgagagtgt ggaggccgac 960
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aagtggatgg cgcctgaggc cttgtttgac cgagtctaca ctcaccagag tgacgtctgg 2040
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cctgtggagg agctcttcaa gctgctgaag gagggccacc gcatggacaa gcccgccaac 2160
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cccaccttca agcagctggt ggaggacctg gaccgtgtcc ttaccgtgac gtccaccgac 2280
gagtacctgg acctgtcggc gcctttcgag cagtactccc cgggtggcca ggacacccca 2340
agctccagct cctcagggga cgactccgtg tttgcccacg acctgctgcc cccggcccca 2400
cccagcagtg ggggctcgcg gacgtga 2427

<210> 15
<211> 2427
<212> ADN

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Mutant N542K FGFR3-IIIb:
(Mutant 2)

<400> 15

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tcctcggagt ccttggggac ggagcagcgc gtcgtggggc gagcggcaga agtcccgggc 120
ccagagcccg gccagcagga gcagttggtc ttcggcagcg gggatgctgt ggagctgagc 180
tgtccccccgc ccgggggtgg tcccatgggg cccactgtct gggtcaagga tggcacaggg 240
ctggtgccct cggagcgtgt cctggtgggg ccccagcggc tgcaggtgct gaatgcctcc 300
cacgaggact ccggggccta cagctgccgg cagcggctca cgcagcgcgt actgtgccac 360
ttcagtgtgc gggtgacaga cgctccatcc tcgggagatg acgaagacgg ggaggacgag 420
gctgaggaca caggtgtgga cacaggggcc ccttactgga cacggcccga gcggatggac 480
aagaagctgc tggccgtgcc ggccgccaac accgtccgct tccgctgccc agccgctggc 540
aaccccactc cctccatctc ctggctgaag aacggcaggg agttccgcgg cgagcaccgc 600
attggaggca tcaagctgcg gcatcagcag tggagcctgg tcatggaaag cgtggtgccc 660
tcggaccgcg gcaactacac ctgcgtcgtg gagaacaagt ttggcagcat ccggcagacg 720
tacacgctgg acgtgctgga gcgctccccg caccggccca tcctgcaggc ggggctgccg 780
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gccgaggagg agctggtgga ggctgacgag gcgggcagtg tgtatgcagg catcctcagc 1140
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cgcagccccc ccaagaaagg cctgggctcc cccaccgtgc acaagatctc ccgcttcccg 1260
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gccgccaagc ctgtcaccgt agccgtgaag atgctgaaag acgatgccac tgacaaggac 1560
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gccaagggta acctgcggga gtttctgcgg gcgcggcggc ccccgggcct ggactactcc 1740
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cctgtggagg agctcttcaa gctgctgaag gagggccacc gcatggacaa gcccgccaac 2160
tgcacacacg acctgtacat gatcatgcgg gagtgctggc atgccgcgcc ctcccagagg 2220
cccaccttca agcagctggt ggaggacctg gaccgtgtcc ttaccgtgac gtccaccgac 2280
gagtacctgg acctgtcggc gcctttcgag cagtactccc cgggtggcca ggacaccccc 2340
agctccagct cctcagggga cgactccgtg tttgcccacg acctgctgcc cccggcccca 2400
cccagcagtg ggggctcgcg gacgtga                                     2427
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<210> 16
<211> 2427
<212> ADN
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Mutant G382R FGFR3-IIIb:
(Mutant 1)

<400> 16

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tcctcggagt ccttggggac ggagcagcgc gtcgtggggc gagcggcaga agtcccgggc 120
ccagagcccg gccagcagga gcagttggtc ttcggcagcg gggatgctgt ggagctgagc 180
tgtcccccgc ccgggggtgg tcccatgggg cccactgtct gggtcaagga tggcacaggg 240
ctggtgccct cggagcgtgt cctggtgggg ccccagcggc tgcaggtgct gaatgcctcc 300
cacgaggact ccggggccta cagctgccgg cagcggctca cgcagcgcgt actgtgccac 360
ttcagtgtgc gggtgacaga cgctccatcc tcgggagatg acgaagacgg ggaggacgag 420
gctgaggaca caggtgtgga cacaggggcc ccttactgga cacggcccga gcggatggac 480
aagaagctgc tggccgtgcc ggccgccaac accgtccgct tccgctgccc agccgctggc 540
aaccccactc cctccatctc ctggctgaag aacggcaggg agttccgcgg cgagcaccgc 600
attggaggca tcaagctgcg gcatcagcag tggagcctgg tcatggaaag cgtggtgccc 660
tcggaccgcg gcaactacac ctgcgtcgtg gagaacaagt ttggcagcat ccggcagacg 720
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gccaaccaga cggcggtgct gggcagcgac gtggagttcc actgcaaggt gtacagtgac 840
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<212> ADN
<213> Artificial Sequence

<220>
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<212> ADN
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```

Claims

1. A method for detecting carcinomas in a biological sample, comprising identifying FGFR3 mutations.

2. The method of claim 1, comprising screening for single nucleotide mutation(s) in nucleic acids of the group comprising genomic DNA, RNA or cDNA.

3. The method of claim 1, comprising screening for single mutation(s) in proteins.

4. The method of claim 1., comprising screening for mutations creating cysteine residues in the extracellular or transmembrane domains of the receptor.

5. The method of claim 1, comprising screening for mutations resulting in at least one amino-acid substitution in the kinase domain of the receptor.

6. The method of claim 5, comprising screening of activating mutation(s) of FGFR3.

7. The method of claim 6, comprising screening of activating mutation(s) of FGFR3-IIIb.

8. The method of claim 1, comprising screening for mutation(s) in the group comprising exon 7, encoding the junction between immunoglobulin-like domains II and III of FGFR3, exon 10, encoding the transmembrane domain, exon 15, encoding the tyrosine kinase domain I, and the exon encoding the C-terminal part.

9. The method of claim 1, comprising screening for missense mutations such as implicated in thanatophoric dysplasia, NSC, achondroplasia, SADDAN, or hypochondroplasia.

10. The method of claim 9, wherein the mutations comprise R248C, S249C, G372C, S373C, Y375C, K652E, K652M, JB09G, J809C, J809R, J809L, P250R, G377C, G382R, A393E, N542K.

11. The method of claim 9, comprising screening R248C, S249C, G372C, K652E and Y375C mutations.

12. The method of claim 1, wherein the biological sample is selected in the group comprising a tissue, bone marrow, or a body fluid.

13. The method of claim 12, wherein said body fluid is selected in the group comprising blood, urine from a warm-blooded animal.

14. The method of claim 13, wherein said body fluid is from a human.

15. The method of claim 1 for detecting human bladder and cervix carcinomas.

16. The method of claim 1, for detecting lung, breast, colon, skin cancers.

17. Use of an antibody directed against FGFR3 for the manufacture of a medicament for treating carcinomas.

18. Use according to claim 17 wherein the antibody is monoclonal.

19. Use according to claim 17 wherein the antibody is humanized.

20. Use of an antisens oligonucleotides directed against a wild type or mutated FGFR3 isoform for the manufacture of a medicament for treating carcinomas.

21. Use according to claims 17 to 20, wherein said carcinomas are cervix or bladder carcinomas.

22. A transgenic animal excluding human comprising a construction which comprises a keratin promoter and cDNA of mutated FGFR3, allowing the expression of a mutated FGFR3 directed in epithelium.

Patentansprüche

1. Verfahren zum Nachweisen von Karzinomen in einer biologischen Probe, umfassend das Identifizieren von FGFR3-Mutationen.

2. Verfahren gemäß Anspruch 1, umfassend das Suchen nach Einzelnucleotidmutationen in Nucleinsäuren der Gruppe, die genomische DNA, RNA oder cDNA umfasst.

3. Verfahren gemäß Anspruch 1, umfassend das Suchen nach Einzelmutationen in Proteinen.

4. Verfahren gemäß Anspruch 1, umfassend das Suchen nach Mutationen, die Cysteinreste in der extrazellulären Domäne oder der Transmembrandomäne des Rezeptors verursachen.

5. Verfahren gemäß Anspruch 1, umfassend das Suchen nach Mutationen, die zu wenigstens einer Aminosäuresubstitution in der Kinasedomäne des Rezeptors führen.

6. Verfahren gemäß Anspruch 5, umfassend das Suchen nach aktivierenden Mutationen von FGFR3.

7. Verfahren gemäß Anspruch 6, umfassend das Suchen nach aktivierenden Mutationen von FGFR3-IIIb.

8. Verfahren gemäß Anspruch 1, umfassend das Suchen nach Mutationen in der Gruppe, die das Exon 7, das die Verknüpfung zwischen den immunglobulinartigen Domänen II und III von FGFR3 codiert, das Exon 10, das die Transmembrandomäne codiert, das Exon 15, das die TyrosinKinase-Domäne I codiert, und das Exon, das den C-terminalen Teil codiert, umfasst.

9. Verfahren gemäß Anspruch 1, umfassend das Suchen nach Fehlsinnmutationen, wie sie bei thanatophorer Dysplasie, NSC, Achondroplasie, SADDAN oder Hypochondroplasie impliziert sind.

10. Verfahren gemäß Anspruch 9, wobei die Mutationen R248C, S249C, G372C, S373C, Y375C, K652E, K652M, J809G, J809C, J809R, J809L, P250R, G377C, G382R, A393E, N542K umfassen.

11. Verfahren gemäß Anspruch 9, umfassend das Suchen nach den Mutationen R248C, S249C, G372C, K652E und Y375C.

12. Verfahren gemäß Anspruch 1, wobei die biologische Probe aus der Gruppe ausgewählt ist, die ein Gewebe, Knochenmark oder eine Körperflüssigkeit umfasst.

13. Verfahren gemäß Anspruch 12, wobei die Körperflüssigkeit aus der Gruppe ausgewählt ist, die Blut und Urin von einem warmblütigen Tier umfasst.

14. Verfahren gemäß Anspruch 13, wobei die Körperflüssigkeit von einem Menschen stammt.

15. Verfahren gemäß Anspruch 1 zum Nachweis von humanem Harnblasen- und Cervixkarzinom.

16. Verfahren gemäß Anspruch 1 zum Nachweis von Lungen-, Brust-, Dickdarm- und Hautkrebs.

17. Verwendung eines gegen FGFR3 gerichteten Antikörpers zur Herstellung eines Medikaments zur Behandlung von Karzinomen.

18. Verwendung gemäß Anspruch 17, wobei der Antikörper monoklonal ist.

19. Verwendung gemäß Anspruch 17, wobei der Antikörper humanisiert ist.

20. Verwendung von Antisense-Oligonucleotiden, die gegen eine Wildtyp- oder mutierte FGFR3-Isoform gerichtet sind, zur Herstellung eines Medikaments zur Behandlung von Karzinomen.

21. Verwendung gemäß Anspruch 17 bis 20, wobei es sich bei den Karzinomen um Cervix- oder Harnblasenkarzinome handelt.

22. Transgenes Tier ausschließlich des Menschen, das ein Konstrukt umfasst, welches einen Keratinpromotor und cDNA von mutiertem FGFR3 umfasst und die Expression eines mutierten FGFR3 erlaubt, der ins Epithel gelenkt wird.

Revendications

1. Procédé de détection de carcinomes dans un échantillon biologique, comprenant l'identification de mutations de FGFR3.

2. Procédé selon la revendication 1, comprenant le criblage d'une ou plusieurs mutations ponctuelles dans des acides nucléiques du groupe comprenant l'ADN génomique, l'ARN ou l'ADNc.

3. Procédé selon la revendication 1, comprenant le criblage d'une ou plusieurs mutations ponctuelles dans des protéines.

4. Procédé selon la revendication 1, comprenant le criblage de mutations créant des résidus cystéine dans les domaines transmembranaires ou extracellulaires du récepteur.

5. Procédé selon la revendication 1, comprenant le criblage de mutations entraînant au moins une substitution d'acide aminé dans le domaine kinase du récepteur.

6. Procédé selon la revendication 5, comprenant le criblage de mutation(s) activatrice(s) de FGFR3.

7. Procédé selon la revendication 6, comprenant le criblage de mutation(s) activatrice(s) de FGFR3-IIIb.

8. Procédé selon la revendication 1, comprenant le criblage de mutation(s) dans le groupe comprenant l'exon 7, qui code pour la jonction entre les domaines II et III de type immunoglobuline de FGFR3, l'exon 10, qui code pour le domaine transmembranaire, l'exon 15, qui code pour le domaine tyrosine-kinase I, et l'exon qui code pour la partie C-terminale.

9. Procédé selon la revendication 1, comprenant le criblage de mutations faux-sens telles que celles impliquées dans la dysplasie thanatophore, NSC, l'achondroplasie, SADDAN ou l'hypochondroplasie.

10. Procédé selon la revendication 9, dans lequel les mutations comprennent R248C, S249C, G372C, S373C, Y375C, K652E, K652M, J809G, J809C, J809R, J809L, P250R, G377C, G382R, A393E et N542K.

11. Procédé selon la revendication 9, comprenant le criblage des mutations R248C, S249C, G372C, K652E et Y375C.

12. Procédé selon la revendication 1, dans lequel l'échantillon biologique est choisi dans le groupe comprenant un tissu, de la moelle osseuse ou un fluide corporel.

13. Procédé selon la revendication 12, dans lequel ledit fluide corporel est choisi dans le groupe comprenant le sang ou l'urine d'un animal à sang chaud.

14. Procédé selon la revendication 13, dans lequel ledit fluide corporel provient d'un être humain.

15. Procédé selon la revendication 1 de détection de carcinomes de cols de l'utérus et de la vessie chez un être humain.

16. Procédé selon la revendication 1 de détection de cancers du poumon, du sein, du colon et de la peau.

17. Utilisation d'un anticorps dirigé contre FGFR3 pour la fabrication d'un médicament pour le traitement de carcinomes.

18. Utilisation selon la revendication 17, dans laquelle l'anticorps est monoclonal.

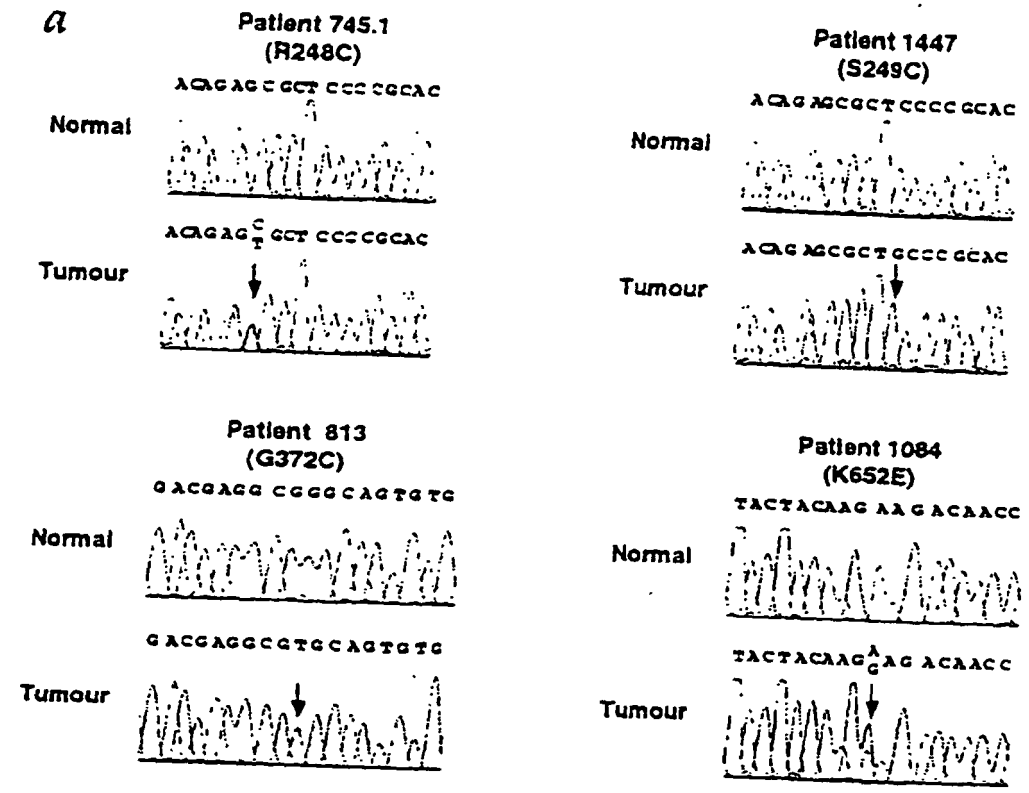
19. Utilisation selon la revendication 17, dans laquelle l'anticorps est humanisé.

20. Utilisation d'oligonucléotides anti-sens dirigés contre une isoforme de FGFR3 mutée ou de type sauvage pour la fabrication d'un médicament pour le traitement de carcinomes.

21. Utilisation selon les revendications 17 à 20, dans laquelle lesdits carcinomes sont des carcinomes du col de l'utérus ou de la vessie.

22. Animal transgénique à l'exclusion d'un être humain comprenant une construction qui comprend un promoteur de la kératine et de l'ADNc de FGFR3 muté permettant l'expression d'un FGFR3 muté dirigée dans l'épithélium.

FIGURE 1


a
Patient 745.1
(R248C)
Normal
Tumour
Patient 1447
(S249C)
Normal
Tumour
Patient 813
(G372C)
Normal
Tumour
Patient 1084
(K652E)
Normal
Tumour

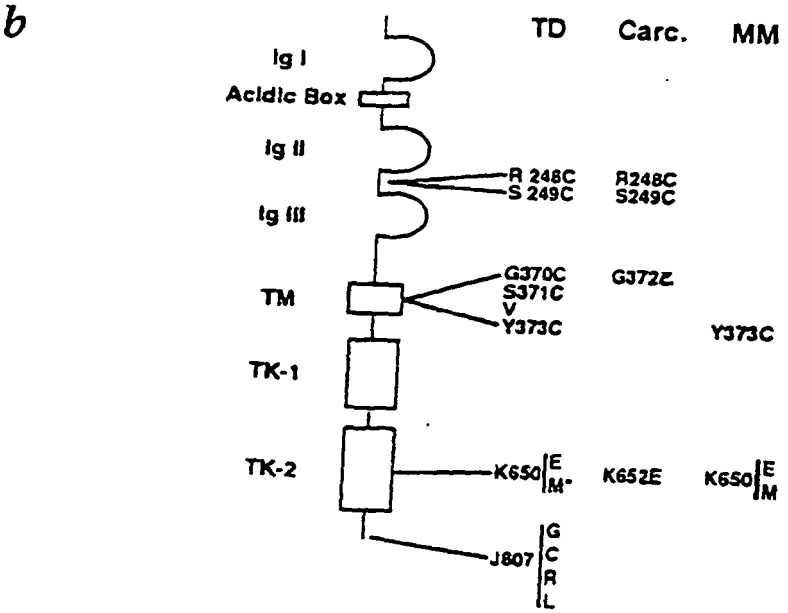

b
TD
Carc.
MM
Ig I
Acidic Box
Ig II
Ig III
TM
TK-1
TK-2
R 248C
S 249C
R248C
S249C
G370C
S371C
V
Y373C
G372E
Y373C
K650 E M
K652E
K650 E M
J807 G C R L

Figure 2A

Wild Type FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
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ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
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TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
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CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2B

Mutant R248C FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
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CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
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CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGTGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
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CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2C

Mutant S249C FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
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CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
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GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
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GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
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GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2D

Mutant G372C FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
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CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
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CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
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AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
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CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
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GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
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CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2E

Mutant K652E FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
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TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
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AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
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GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGGAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2F

Mutant S373C FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCTGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2G

Mutant Y375C FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTGTGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2H

Mutant K652M FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGATGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2I

Mutant X809C FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGC

Figure 2J Mutant 1

Mutant X809G FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGGGA

Figure 2K Mutant 2

Mutant X809G FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGAGA

Figure 2L Mutant 3

Mutant X809G FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGCGA

Figure 2M

Mutant X809L FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTTA

Figure 2N Mutant 1

Mutant N542K FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAAACTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 20 Mutant 2

Mutant N542K FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCGTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2P Mutant 1

Mutant G382R FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACAGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2Q Mutant 2

Mutant G382R FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACCGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2R

Mutant G377C FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCATGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2S

Mutant A393E FGFR3-IIIb:

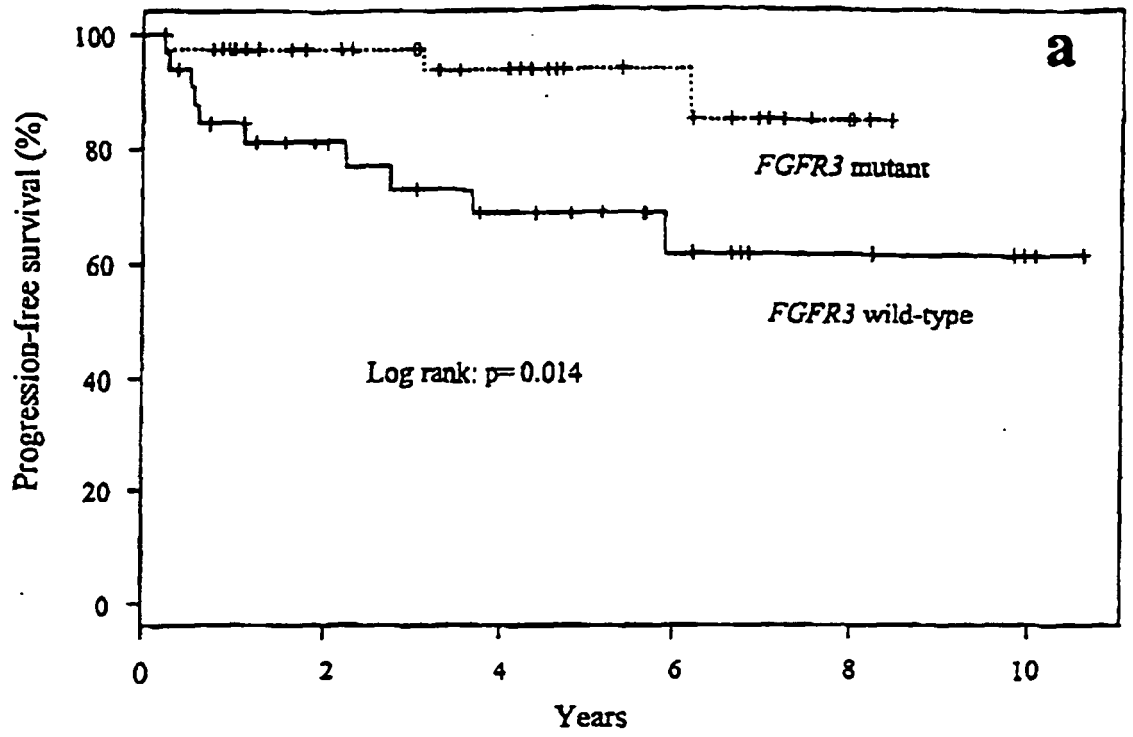
ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGAGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

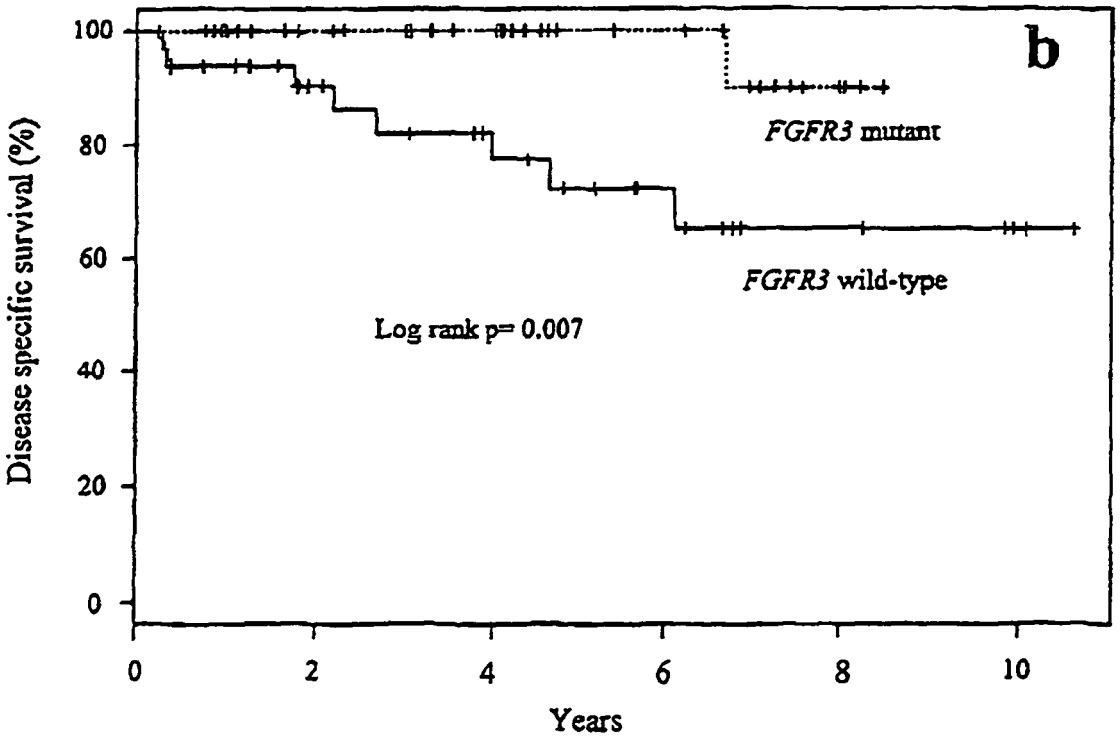
Figure 2T

Mutant P250R FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCGGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCCACGACCTGCTGCCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

FIGURE 3


a
Progression-free survival (%)
100
80
60
40
20
0
0
2
4
6
8
10
Years
FGFR3 mutant
FGFR3 wild-type
Log rank: p= 0.014


b
Disease specific survival (%)
100
80
60
40
20
0
0
2
4
6
8
10
Years
FGFR3 mutant
FGFR3 wild-type
Log rank p= 0.007